Japanese Kokai Patent Application Hei 5[1993]-9197

Translated from Japanese by the Ralph McElroy Co., Custom Division
P.O. Box 4828, Austin, Texas 78765 USA

Code: 2429-67913

JAPANESE PATENT OFFICE

PATENT JOURNAL

KOKAI PATENT APPLICATION NO. Hei 5[1993]-9197

Technical Disclosure Section

Int.Cl.[5]:	C 07 H 19/167 //A 61 K 31/70
Sequence Nos. for Office Use:	7822-4C 8314-4C 8314-4C
Application No.:	Hei 3[1991]-158991
Application Date:	June 28, 1991
Publication Date:	January 19, 1993
Examination Request:	Not requested
Number of Claims:	1 (Total of 8 pages)

2-ALKYNYLADENOSINE DERIVATIVE

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Abstract

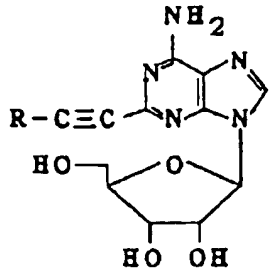
Objective

To offer a novel compound that has few side effects such as cardiac suppression, while having excellent effects as a circulation-improving drug with hypotensive effects and high selectivity with respect to the A_2 receptor.

Constitution

The novel compounds of the present invention comprise the 2-alkynyladenosine derivatives expressed by formula (I) and salts thereof.

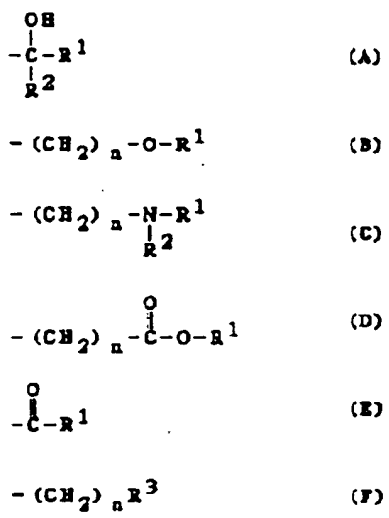
Structure I



(I)

In the formula, R denotes any of the structures of formulae (A)-(F).

Structure 2



(A)

(B)

(C)

(D)

(E)

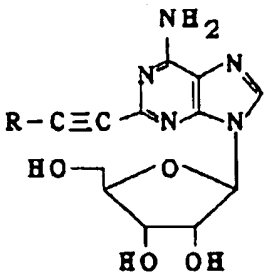
(F)

(in the formulae, R^1 and R^2 can be the same or different, and denote hydrogen atoms or alkyl groups, n denotes an integer of 0-10, and R^3 denotes an alkenyl group, alkynyl group, aryl group, azido group or cyano group).

Claim

The 2-alkynyladenosine derivatives expressed by formula (I) and salts thereof:

Structure 1

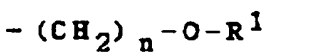


(I)

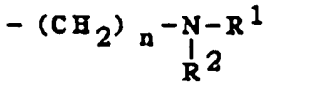
in the formula, R denotes any of the structures of formulae (A)-(F):

Structure 2

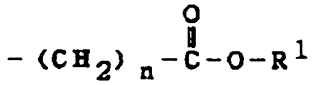
(A)



(B)



(C)



(D)

(E)

(F)

(in the formulae, R^1 and R^2 can be the same or different, and denote hydrogen atoms or alkyl groups, n denotes an integer of 0-10, and R^3 denotes an alkenyl group, alkynyl group, aryl group, azido group or cyano group).

Detailed description of the invention

[0001]

Industrial utilization field

The present invention concerns a novel 2-alkynyladenosine derivative.

[0002]

Prior technology and problems to be solved by the invention

In the past, adenosine has been known to have a blood platelet aggregation inhibitory effect and a strong hypotensive effect, but these activities are not persistent. Moreover, this substance has an inhibitory effect with respect to the heart (e.g. decreases heart rate), and also has the side effect of a central inhibitory effect. Consequently, it is necessary to solve these problems if adenosine or its derivatives are to be used as therapeutics for sufferers of hypertension or stenocardia. Various 2-substituted adenosine derivatives have been synthesized in the attempt to solve these types of problems (Chem. Pharm. Bull. 23(4), 759-774 (1975), Japanese Kokai Patent Application No. Hei 1[1989]-265100), but these derivatives have not provided

adequate solutions to the aforementioned types of problems, and the realization of a medical drug has not yet occurred.

[0003]

The inventor et al. of the present invention have previously succeeded in synthesizing compounds wherein specific alkyl groups having linear carbon chains are introduced at the second position of adenosine (Chem. Pharm. Bull. 33(4), 1766-1769 (1985)), and these compounds were discovered to exhibit little effect on heart rate while also providing dramatic and continued hypotensive effects (for example, Nucleic Acids Research, Symposium Series No. 16, 97-100 (1985), Japanese Kokoku Patent No. Hei 1[1989]-33477, and Japanese Kokoku Patent No. Hei 2[1990]-17526)). These types of 2-alkynyladenosines having linear carbon chains, in comparison to other conventional adenosine derivatives, had weak side effects along with a persistent pharmacological action on the circulatory system, but the discovery of compounds with further enhancement in these characteristics is desired.

[0004]

In recent years, it has been reported that hypotensive action and blood platelet aggregation inhibition are expressed via the adenosine A_2 receptor (referred to below as "A_2 receptor"), whereas it has also been reported that a cardiac inhibitory action and central inhibitory action are manifested via the adenosine A_1 receptor (referred to below as "A_1 receptor"). For example, 5'-N-ethylcarboximidoadenosine (NECA)

(Archs. Pharmacodyn. 203, 140-149 (1977)) is known to be a compound that has high affinity for the A_2 receptor, and is used as a ligand for binding assays (Mol. Pharmacol. 29, 331-346 (1986)). However, because the compound has high affinity for the A_1 receptor, it readily produces the aforementioned types of side effects, and cannot be used as a therapeutic drug. Consequently, if an adenosine derivative were developed that has low affinity for the A_1 receptor but high affinity for the A_2 receptor, then this compound might be effective as a drug that could be used in the treatment or prevention of hypertension, ischemic heart disease, ischemic brain disease and other circulatory diseases.

[0005]

Specifically, the objective of the present invention is to offer a novel 2-alkynyladenosine derivative with little side effects such as heart inhibition or central inhibition, while having high affinity with respect to the A_2 receptor, and providing continuous pharmacological action in terms of hypertension, coronary vasodilation, peripheral system vasodilation, brain circulation improvement, peripheral circulation improvement and platelet aggregation inhibition.

[0006]

Means for solving the problems

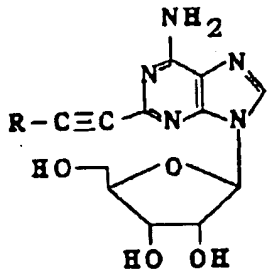
The inventor et al. of the present invention developed novel 2-alkynyladenosine derivatives, and during the course of various investigations into their pharmacological activities, discovered

that specific 2-alkynyladenosine derivatives have high affinity with respect to the A_2 receptor and low affinity with respect to the A_1 receptor, or in other words, have high selectivity with respect to the A_2 receptor. The inventors of the present invention thus perfected the present invention upon confirming that these compounds are effective as drugs for diseases related to the circulatory system.

[0007]

Specifically, the present invention is a 2-alkynyladenosine derivative expressed by formula (I) and salts thereof (referred to below as "compounds of the present invention").

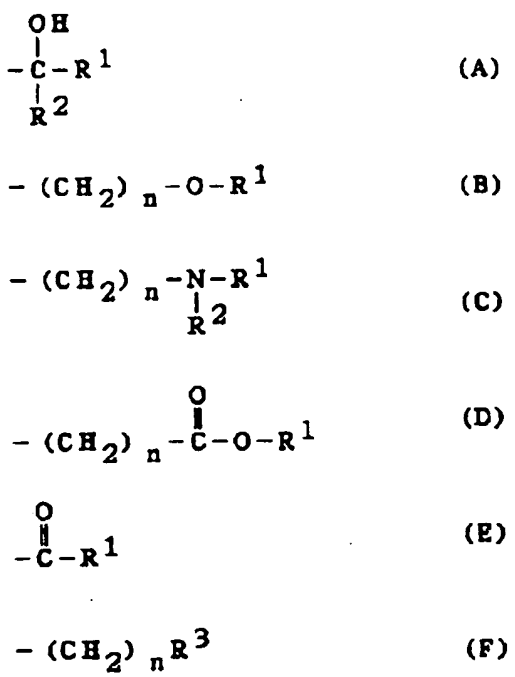
Structure 3



(I)

In the formula, R denotes any of the structures of formulae (A)-(F):

Structure 4



(A)

(B)

(C)

(D)

(E)

(F)

(in the formulae, R^1 and R^2 can be the same or different, and denote hydrogen atoms or alkyl groups, n denotes an integer of 1-10, and R^3 denotes an alkenyl group, alkynyl group, aryl group, azido group or cyano group).

[0008]

1. Compounds of the present invention

The compounds of the present invention are compounds wherein R in formula I above denotes any of the formulae (A)-(F).

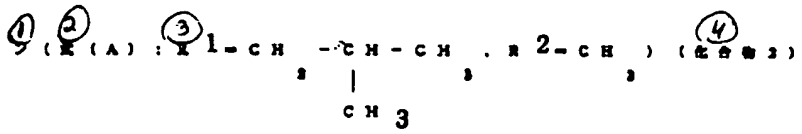
Examples of the alkyl groups expressed by R^1 and R^2 in formulas (A)-(E) that can be cited are linear or branched chains with carbon numbers of 1-10. Examples of aryl groups expressed by R^3 in the formula (F) that can be cited include phenyl, tolyl and naphthyl groups. In addition, examples of alkenyl groups and alkynyl groups denoted by R^3 that can be cited are groups with carbon numbers of 1-10. The alkenyl groups, alkynyl groups or aryl groups that are denoted by R^3 and the alkyl groups that are denoted by R^1 and R^2 above can have one or a number of substituents at any position, examples of which include halogen atoms, alkyl groups, alkoxy groups, hydroxyl groups, carbonyl groups and alkoxycarbonyl groups.

[0009]

Typical examples of the 2-alkynyladenosine derivatives expressed by general formula (I) are presented below.

[0010]

(1) 2-(3-hydroxy-3-methyl-1-butynyl)adenosine (formula (A): R^1 = R^2 = CH_3) (compound 1)
(2) 2-(3,5-dimethyl-3-hydroxy-1-hexynyl)adenosine



Key: 1 N 3 formula
2 and 4 (compound 2)

(3) 2-(3-hydroxy-1-octynyl)adenosine (formula (A): $R^1 = (CH_2)_4CH_3$, R^2 = H) (compound 3)

(4) 2-(3-methoxy-1-propynyl)adenosine (formula B: $R^1 = CH_3$, n = 1) (compound 4)

(5) 2-(3-n-butoxy-1-propynyl)adenosine (formula B: $R^1 = (CH_2)_3CH_3$, n = 1) (compound 5)

(6) 2-(4-n-propoxy-1-butynyl)adenosine (formula (B): $R^1 = (CH_2)_2CH_3$, n=2) (compound 6)

(7) 2-(5-ethoxy-1-pentynyl)adenosine (formula (B): $R^1 = CH_2CH_3$, n = 3) (compound 7)

(8) 2-(4-n-octoxy-1-butynyl)adenosine (formula (B): $R^1 = (CH_2)_7CH_3$, n=2) (compound 8)

(9) 2-(6-hydroxy-1-hexynyl)adenosine (formula (B): R^1 = H, n = 4) (compound 9)

(10) 2-(3-dimethylamino-1-propynyl)adenosine (formula (C): $R^1 = R^2 = CH_3$, n = 1) (compound 10)

(11) 2-(6-amino-1-hexynyl)adenosine (formula (C): $R^1 = R^2$ = H, n = 4) (compound 11)

(12) 2-(7-carboxy-1-heptynyl)adenosine (formula (D): R^1 = H, n = 5) (compound 12)

(13) 2-(5-carboxy-1-pentynyl)adenosine (formula (D): R^1 = h, n = 3) (compound 13)

(14) 2-(4-ethoxycarbonyl-1-butynyl)adenosine (formula (D): $R^1 = CH_2CH_3$, n = 2) (compound 14)

(15) 2-(3-oxo-1-octynyl)adenosine (formula (E): $R^1 = (CH_2)_4CH_3$) (compound 15)

(16) 2-(6-phenyl-1-hexynyl)adenosine (formula (F): R^3 = phenyl, n = 4) (compound 16)

(17) 2-(6-(4-ethoxycarbonyl)phenyl-1-hexynyl)adenosine (formula (F): R^3 = 4-ethoxycarbonylphenyl, n = 4) (compound 17)

(18) 2-(4-phenyl-1-butynyl)adenosine (formula (F): R^3 = phenyl, n = 2) (compound 18).
(19) 2-(6-azido-1-hexynyl)adenosine (structure (F): R^3 = azido, n = 4) (compound 19)
(20) 2-(5-cyano-1-pentynyl)adenosine (formula (F): R^3 = cyano, n = 3) (compound 20)
(21) 2-(4-(p-toluyl)-1-butynyl)adenosine (formula (F): R^3 = p-tolyl, n = 2) (compound 21)
(22) 2-(4-(o-chlorophenyl)-1-butynyl)adenosine (formula (F): R^3 = o-chlorophenyl, n = 2) (compound 22)
(23) 2-(4-(p-methoxyphenyl)-1-butynyl)adenosine (formula (F): R^3 = p-methoxyphenyl, n = 2) (compound 23)
(24) 2-(1,7-decadiynyl)adenosine (formula F: R^3 = $CH_3CH_2{\equiv}C$, n = 4) (compound 24)
(25) 2-(branynyl [transliteration])adenosine (formula (F): R^3 = $CH_2{=}CH$, n = 0) (compound 25)

[0011]

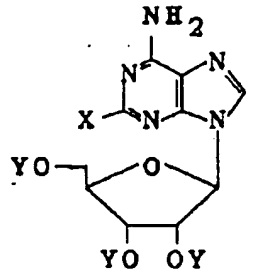
The compounds of the present invention can exist in their free forms or as salts. Examples of salts include inorganic acid salts such as hydrochlorides, sulfates and borohydrides, organic acid salts such as oxalates, citrates, and malates and other acid addition salts; sodium salts, potassium salts and other alkali metal salts; calcium salts, barium salts, magnesium salts and other alkaline earth metal salts; and ammonium salts. Of these salts, those salts that are pharmacologically acceptable are preferred, such as hydrochlorides, oxalates, citrates, malates and sodium salts.

[0012]

2. Manufacture of the compounds of the present invention

The compounds of the present invention can be prepared, for example, by allowing a reaction to occur (cross-coupling) between a 2-halogenoadenosine compound expressed by formula (II)

Structure 5



(II)

(in the formula, X denotes an iodine atom or bromine atom, and Y denotes a hydrogen atom or a hydroxyl protecting group)
and the acetylene compound expressed by formula (III)

$$R\text{-}C{\equiv}CH \qquad \text{(III)}$$

(in the formula, R denotes the same as above)
in the presence of a palladium catalyst and copper compound in solvent, followed by removal of the hydroxyl protecting group.

[0013]

There are no particular restrictions on the hydroxyl protecting group expressed by Y, and any group that is commonly used as a nucleoside hydroxyl protecting group can be used. Specific examples that can be cited include acetyl, chloroacetyl, dichloroacetyl, trifluoroacetyl, methoxyacetyl, propionyl, n-butyryl, (E)-2-methylbutenoyl, isobutyryl, pentanoyl, benzoyl, o-(dibromomethyl)benzoyl, o-(methoxycarbonyl)benzoyl, p-phenylbenzoyl, 2,4,6-trimethylbenzoyl, p-toluoyl, p-anisoyl, p-chlorobenzoyl, p-nitrobenzoyl, a-naphthoyl and other acyl groups; benzyl, phenethyl, 3-phenylpropyl, p-methoxybenzyl, p-nitrobenzyl, o-nitrobenzyl, p-halobenzyl, p-cyanobenzyl, diphenylmethyl, triphenylmethyl(trityl), α or β-naphthylmethyl, α-naphthyldiphenylmethyl and other aralkyl groups; trimethylsilyl, triethylsilyl, dimethylisopropylsilyl, isopropyldimethylsilyl, methyldi-t-butylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, triisopropylsilyl, tetraisopropyldisiloxanyl and other silyl groups; methoxymethyl, ethoxymethyl and other alkoxymethyl groups; isopropylidene, ethylidene, propylidene, benzylidene, methoxymethylidene and other acetal-type or ketal-type protecting groups. The introduction of this type of protecting group can be carried out by a common method.

[0014]

R of the acetylene compound expressed by formula (III) is selected so that it corresponds to the R of the compound of formula (I) which is the target of synthesis. This type of

acetylene compound is commercially available, but the substance can also be readily prepared by the appropriate application of common synthesis methods for organic compounds.

[0015]

The cross-coupling reaction between the compound of formula (II) and the compound of formula (III) should be carried out according to known synthesis methods for 2-alkynyladenosines (Japanese Kokoku Patent Nos. Hei 1[1989]-33477 and Hei 2[1990]-17526).

[0016]

Examples of reaction solvents include triethylamine, tributylamine, N,N-diisopropylethylamine, trioctylamine, N,N,N',N'-tetramethyl-1,8-naphthalenediamine, N,N-dimethylaniline, N,N-diethylaniline, pyridine and other basic solvents alone, or mixed solvents consisting of these basic solvents and aprotic polar solvents such as acetonitrile, N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), N,N-dimethylacetamide, tetrahydrofuran (THF) and 1,4-dioxane.

[0017]

Examples of palladium catalysts include bis(acetonitrile)palladium dichloride, bis(triphenylphosphine)palladium dichloride, bis(benzonitrile)palladium dichloride, tetrakis(triphenylphosphine)palladium and

bis(triphenylphosphine)palladium diacetate. In addition, of the aforementioned palladium catalyst, bis(triphenylphosphine)palladium dichloride or bis(triphenylphosphine)palladium diacetate can be used without modification in the form of materials generated by adding palladium chloride or palladium diacetate and triphenylphosphine separately to the reaction solution. It is sufficient to use the palladium catalyst in approximately a catalytic amount, or about 0.001-0.1x by mole with respect to one mole of the compound expressed by formula (II). The copper compound is added to the reaction solution in order to promote the cross-coupling reaction with the palladium catalyst. For example, copper I iodide, copper I bromide or other copper halide compound can be added to the reaction solution at about 0.06x by mole with respect to one mole of compound of formula (II).

[0018]

The cross-coupling reaction can be carried out by means of using 1-3x by mole of acetylene compound with respect to one mole of 2-halogenoadenosine compound in the presence of the palladium catalyst and copper compound, and carrying out the reaction for 1-100 h at a reaction temperature of 10-130°C. After completion of the cross-coupling reaction, the isolation and purification of the resulting compound can be carried out by employing a common isolation and purification means for nucleosides (e.g. adsorption chromatography treatment, or recrystallization). The copper compound can also be separated from the reaction solution by a hydrogen sulfide treatment or organic solvent-water extraction

distribution treatment carried out in an appropriate combination as necessary.

[0019]

Next, when the hydroxyl protective groups are to be removed, this may be carried out according to a common method. For example, when the protective group is an acetal type or ketal type protective group, the protective groups can be eliminated by hydrolysis using trifluoroacetic acid, trichloroacetic acid, acetic acid, formic acid, sulfuric acid, hydrochloric acid or other acids. In addition, when the protective group is a silyl group, the protective groups can be eliminated by using trifluoroacetic acid, trichloroacetic acid, tosylic acid [sic; possibly, "p-toluenesulfonic acid"], sulfuric acid, hydrochloric acid or other acid, tetrabutyl ammonium fluoride, hydrogen fluoride pyridine salt or ammonium fluoride in an appropriate solvent (e.g. THF, DMSO, acetonitrile or 1,4-dioxane). Moreover, when the protective group is an acyl group, the protective groups can be eliminated by hydrolysis using methanolic ammonia, concentrated ammonia aqueous solution, sodium methoxide, sodium ethoxide, sodium hydroxide or potassium hydroxide.

[0020]

Application examples

The present invention is described in detail below using application examples.

Application Examples 1-21

786 mg (2 mmol) of 2-iodoadenosine were dissolved in 10 mL of DMF. 70 mg of bis(triphenylphosphine)palladium dichloride, 38 mg of copper (I) iodide, 1.4 mL of triethylamine and 2-5 mmol of various acetylene compounds (compounds of formula (III)) were added, and a reaction was allowed to occur at 70-120°C.

[0021]

After the reaction, the solution was concentrated under reduced pressure, the residue was dissolved in methanol, and hydrogen sulfide was passed through the solution for 1 min. The precipitated sediment was then filtered, and the resulting filtrate was concentrated to dryness under reduced pressure. The residue was then purified by silica gel column chromatography to obtain 21 types of target compound.

[0022]

(1) 2-(3-hydroxy-3-methyl-1-butynyl)adenosine (compound 1)

m.p.: 142-147°C
^{1}H-NMR (DMSO-d_6) δ: 1.46 (6H, s, CH_3 x 2), 3.40-3.69 (1H, m, H-5'), 3.94 (1H, m, H-4'), 4.12 (2H, dd, H-3'), 4.48 (1H, dd, H-2'), 5.1-5.2 (2H, m, OH x 2), 5.4 (1H, d, OH), 5.5 (1H, s, C≡CCOH), 5.87 (1H, d, H-1', J = 6.35 Hz), 7.4 (2H, s, NH_2), 8.41 (1H, s, H-8)

[0023]

(2) 2-(3,5-dimethyl-3-hydroxy-1-hexynyl)adenosine (compound 2)

^{1}H-NMR ($CDCl_3$-DMSO-d_6) δ: 0.98 (6H, d, J = 6 Hz, $(CH_3)_2$), 1.50 (3H, s, CH_3), 1.62 (2H, bs, CH_2), 1.70-2.05 (1H, m, CH), 3.66-4.06 (3H, m, H-5', H-4'), 4.66 (1H, m, H-3'), 4.95 -5.32 (1H, m, H-2'), 5.85 (1H, d, J = 6Hz, H-1'), 6.04 (1H, br, OH), 7.10-7.80 (2H, br, NH_2), 7.97 (1H, s, H-8)

[0024]

(3) 2-(3-hydroxy-1-octynyl)adenosine (compound 3)

m.p.: 177-179°C
^{1}H-NMR (DMSO-d_6) δ: 0.91 (3H, t, CH_3), 1.69 (8H, m, (CH_2) x 4), 3.56-3.72 (2H, m, H-5'), 3.98 (1H, m, H-4'), 4.16 (1H, dd, H-3'), 4.40 (1H, dd, CHC≡C), 4.51 (1H, dd, H-2'), 5.1, 5.2, 5.4, 5.5 (4H, brs (each), OH x 4), 5.89 (1H, d, H-1', J = 5.86 Hz), 7.38 (2H, s, NH_2), 8.39 (1H, s, H-8)

[0025]

(4) 2-(3-methoxy-1-propynyl)adenosine (compound 4)

m.p.: 118-123°C
^{1}H-NMR (DMSO-d_6) δ: 3.35 (3H, t, CH_3), 3.54-3.70 (2H, m, H-5'), 3.96 (1H, m, H-4'), 4.13 (1H, dd, H-3'), 4.32 (2H, s, $CH_2C{\equiv}C$), 4.55 (1H, dd, H-2'), 5.2, 5.5 (3H, s (each), OH x 3), 5.87 (1H, d, H-1', J = 5.93 Hz), 7.5 (2H, s, NH_2), 8.43 (1H, s, H-8')

[0026]

(5) 2-(3-n-butoxy-1-propynyl)adenosine (compound 5)

m.p.: 105-110°C
^{1}H-NMR (DMSO-d_6) δ: 0.90 (3H, t, CH_3), 1.34 , 1.52 (4H, m (each), CH_2 x 2), 3.51 (2H, t, CH_2O), 3.62 (2H, m, H-5'), 3.95 (1H, m, H-4'), 4.13 (1H, dd, H-3'), 4.35 (2H, s, $OCH_2C{\equiv}C$), 4.54 (1H, dd, H-2'), 5.2 (2H, brs, OH x 2), 5.5 (1H, brs, OH), 5.86 (1H, d, H-1', J = 5.93 Hz), 8.43 (1H, s, H-8)

[0027]

(6) 2-(4-n-propoxy-1-butynyl)adenosine (compound 6)

^{1}H-NMR (DMSO-d_6) δ: 0.87 (3H, t, CH_3), 1.53 (2H, m, $MeC\underline{H}_2$), 2.65 (2H, t, $CH_2C{\equiv}C$), 3.38-3.69 (6H, m, H-5', $C\underline{H}_2OC\underline{H}_2$), 3.95 (1H, m, H-4'), 4.12 (1H, dd, H-3'), 4.52 (1H, dd, H-2'), 5.17-5.23 (2H, m, OH x 2), 5.46 (1H, d, OH), 5.86 (1H, d, H-1', J = 6.27 Hz), 7.4 (2H, s, NH_2), 8.42 (1H, s, H-8)

[0028]

(7) 2-(5-ethoxy-1-pentynyl)adenosine (compound 7)

^{1}H-NMR (DMSO-d_6) δ: 1.12 (3H, t, CH_3), 1.76 (2H, t, OCH_2CH_2), 2.44 (2H, t, $CH_2C{\equiv}C$), 3.42-3.70 (6H, m, H-5', $C\underline{H}_2OC\underline{H}_2$), 3.95 (1H, m, H-4'), 4.13 (1H, brs, H-3'), 4.54 (1H, brs, H-2'), 5.2, 5.25 (2H, brs (each), OH x 2), 5.5 (1H, brs, OH), 5.85 (1H, d, H-1',

J = 6.27 Hz), 7.4 (2H, s, NH_2), 8.39 (1H, s, H-8)

[0029]

(8) 2-(4-n-octoxy-1-butynyl)adenosine (compound 8)

^{1}H-NMR (DMSO-d_6) δ: 0.84 (3H, t, CH_3), 1.23-1.47 (12H, m, (CH_2 x 6), 2.63 (2H, t, $CH_2C{\equiv}C$), 3.42 (2H, t, $OCH_2CH_2C{\equiv}C$), 3.53-3.69 H H_2 (4H, H-5', CH_2O), 3.96 (1H, m, H-4'), 4.14 (1H, dd, H-3'), 4.52 (1H, dd, H-2'), 5.1, 5.2 (2H, brs (each), OH x 2), 5.4 (1H, d, OH), 5.87 (1H, d, H-1', J = 5.86 Hz), 7.4 (2H, s, NH_2), 8.39 (1H, s, H-8)

[0030]

(9) 2-(6-hydroxy-1-hexynyl)adenosine (compound 9)

m.p.: 103-107°C
^{1}H-NMR ($CDCl_3$-DMSO-d_6) δ: 1.50-1.83 (4H, m, $-CH_2CH_2-$), 2.23-2.50 (2H, m, CH_2), 3.53-3.93 (4H, m, H-5', OH x 2), 4.07-4.43 (3H, m, H-4', H-3'), 4.80-5.08 (1H, br, H-2'), 5.28 (1H, bs, OH), 5.82 (1H, d, J = 6 Hz, H-1'), 6.30-6.52 (1H, m, OH), 6.97 (2H, bs, NH_2), 7.92 (1H, s, H-8)

[0031]

(10) 2-(3-dimethylamino-1-propynyl)adenosine (compound 10)

m.p.: 199-200°C (decomposition)
^{1}H-NMR (DMSO-d_6) δ: 2.25 (6H, s, CH_3 x 2), 3.45 (2H, s, $CH_2C{\equiv}C$), 3.54-3.68 (2H, m, H-5'), 3.95 (1H, m, H-4'), 4.13 (1H, m, H-3'), 4.54 (1H, dd, H-2'), 5.2, 5.5 (3H, brs (each), OH x 3), 5.89 (1H, d, H-1', J = 5.86 Hz), 7.5 (2H, s, NH_2), 8.40 (1H, s, H-8)

[0032]

(11) 2-(6-amino-1-hexynyl)adenosine (compound 11)
Expressing data as 2',3',5'-tri-O-acetate product

^{1}H-NMR ($CDCl_3$) δ: 8.02 (1H, s, H-8), 7.71-7.51 (1H, m, 6''-NH), 6.29 (1H, d, H-1', J1', 2' = 5.9 Hz), 5.89 (2H, brs, 6-NH_2), 5.85-5.80 (1H, m, H-2'), 5.72-5.60 (1H, m, H-3'), 4.51-4.43 (3H, m, H-4', H-5'a, H-5'b), 3.64-3.60 (2H, m, H-6''), 2.58-2.41 (2H, m, H-3''), 2.15 (6H, s, acetyl x 2), 2.05 (3H, s, acetyl), 1.70-1.50 (4H, m, H-4'', H-5'')

[0033]

(12) 2-(7-carboxy-1-heptynyl)adenosine (compound 12)

^{1}H-NMR (DMSO-d_6) δ: 1.39-1.55 (6H, m, methylene), 2.13 (2H, t, methylene), 2.39 (2H, t, methylene), 3.52-3.68 (2H, m, H-5'), 3.94 (2H, dd, H-4'), 4.13 (1H, t, H-3'), 4.54 (1H, t, H-2'), 5.85 (1H, d, H-1'), 8.38 (1H, s, H-8)

[0034]

(13) 2-(5-carboxy-1-pentynyl)adenosine (compound 13)

^{1}H-NMR (DMSO-d_6) δ: 1.75-1.80 (2H, m, methylene), 2.34 (2H, t, methylene), 2.45 (2H, t, methylene), 3.57-3.70 (2H, m, H-5'), 3.96 (2H, dd, H-4'), 4.14 (1H, t, H-3'), 4.54 (1H, dd, H-2'), 5.23 (1H, d, OH), 5.26 (1H, t, OH), 5.49 (1H, d, OH), 5.85 (1H, d, H-1'), 7.41 (2H, bs, NH_2), 8.40 (1H, s, H-8)

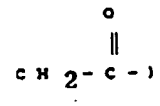
[0035]

(14) 2-(4-ethoxycarbonyl-1-butynyl)adenosine (compound 14)

m.p.: 103-106°C
^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J = 7 Hz, CH_3), 2.04 (3H, bs, OH x 2), 2.52 (4H, s, -CH_2CH_2-), 3.62-3.94 (2H, m, H-5'), 4.30 (2H, bs, H-4', H-3'), 4.17 (2H, q, J = 7 Hz, CH_2), 5.10-5.40 (1H, m, H-2'), 5.88 (1H, d, J = 5 Hz, H-1'), 7.79 (1H, s, H-8)

[0036]

(15) 2-(3-oxo-1-octynyl)adenosine (compound 15)
^{1}H-NMR (DMSO-d_6) δ: 0.88 (3H, t, CH_3), 1.23-1.37 (4H, m, CH_2 x 2), 1.65 (2H, hcp, CH_2), 2.71 (2H, t,



3.57-3.75 (2H, m, H-5'), 3.95-3.97 (1H, m, H-4'), 4.14 (1H, dd, H-3'), 4.52 (1H, dd, H-2'), 5.12 (1H, t, OH), 5.19 (1H, d, OH), 5.48 (1H, d, OH), 5.89 (1H, d, H-1'), 7.68 (2H, bs, NH_2), 8.52 (1H, s, H-8)

[0037]

(16) 2-(6-phenyl-1-hexynyl)adenosine (compound 16)

m.p.: 201-203°C
^{1}H-NMR ($CDCl_3$-DMSO-d_6) δ: 1.50-1.93 (4H, m, $-CH_2CH_2-$), 2.27-2.75 (4H, m, CH_2 x 2), 3.60-3.87 (2H, m, H-5'), 4.06-4.95 (4H, m, H-4', H-3', OH x 2), 5.11 (1H, bd, H-2'), 5.56-5.79 (1H, m, OH), 5.88 (1H, d, J = 6 Hz, H-1'), 6.56 (2H, bs, NH_2), 7.19 (5H, s, phenyl), 8.05 (1H, s, 8-H)

[0038]

(17) 2-(6-(4-ethoxycarbonyl)phenyl-1-hexynyl)adenosine (compound 17)

m.p.: 93-96°C
^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, t, J = 8 Hz, CH_3), 1.20-1.86 (4H, m, $-CH_2CH_2-$), 1.90-2.40 (2H, m, CH_2), 2.66 (2H, t, J = 6 Hz, $PhCH_2-$),

3.55-3.86 (3H, m, H-5', H-4'), 4.27 (4H, m, H-3', OH x 3), 4.33 (2H, q, J = 8 Hz, CH_2), 5.18 (1H, br, H-2'), 5.73 (1H, d, J = 6 Hz, H-1'), 6.80-7.50 (2H, br, NH_2), 7.18 , 7.88 (4H, dd, J = 9 Hz, phenyl), 7.66 (1Hs, H-8)

[0039]

(18) 2-(4-phenyl-1-butynyl)adenosine (compound 18)

m.p.: 115-120°C
^{1}H-NMR (DMSO-d_6) δ: 2.71 (2H, t, $CH_2C{\equiv}C$), 2.87 (2H, t, $PhC\underline{H}_2$), 3.54-3.67 (2H, m, H-5'), 3.95 (1H, m, H-4'), 4.13 (1H, dd, H-3'), 4.54 (1H, dd, H-2'), 5.85 (1H, d, H-1', J = 5.86 Hz), 7.20-7.33 (5H, m, phenyl), 7.42 (2H, brs, NH_2), 8.40 (1H, s, H-8)

[0040]

(19) 2-(6-azido-1-hexynyl)adenosine (compound 19)
^{1}H-NMR ($CDCl_3$) δ: 8.38 (1H, s, H-8), 7.36 (2H, brs, 6-NH_2), 5.85 (1H, d, H-1', J1', 2' = 6.6 Hz), 5.38 (1H, d, 2'-OH, J2'OH, 2'=6.0 Hz), 5.17 (1H, dd, 5'-OH, J5'OH, 5' = 6.6 Hz), 5.10 (1H, d, 3'-OH, J3'OH, 3' = 4.9 Hz), 4.53 (1H, ddd, H-2', J2', 1' = 6.6 Hz, J2', 2'OH = 6.0 Hz, J2', 3' = 5.5 Hz), 4.13 (1H, ddd, H-3', J3', 2' = 5.5 Hz, J3', 3'OH = 4.9 Hz, J3', 4' = 3.3 Hz), 3.95 (1H, ddd, H-4', J4', 3' = 3.3 Hz, J4', 5'a = 3.9 Hz, J4', 5'b = 3.9 Hz), 3.67 (1H, ddd, H-5'a, J5'a, 4' = 3.9 Hz, J5'a, 5'b = 12.1 Hz, J5'a, 5'OH = 6.6 Hz), 3.56 (1H, ddd, H-5'b, J5'b, 4' = 3.9 Hz, J5'b, 5'a = 12.1 Hz, J5'b, 5'OH = 6.6 Hz), 3.40 (2H, t, H-6''), 2.44 (2H, t, H-3''), 1.76-1.57 (4H, m, H-4'', H-5'')

[0041]

(20) 2-(5-cyanol-pentynyl)adenosine (compound 20)

m.p.: 113-115°C
^{1}H-NMR (DMSO-d_6) δ: 1.88 (2H, m, CH_2), 2.51-2.66 (4H, m, $CH_2C{\equiv}C$, $NCCH_2$), 3.63 (2H, m, H-5'), 3.99 (1H, m, H-4'), 4.15 (1H, dd, H-3'), 4.55 (1H, dd, H-2'), 5.14 (1H, d, OH), 5.34 (1H, dd, OH), 5.42 (1H, d, OH), 5.87 (1H, d, H-1', J = 6.35 Hz), 7.41 (2H, s, NH_2), 8.37 (1H, s, H-8)

[0042]

(21) 2-(1,7-decadiynyl)adenosine (compound 24)

m.p.: 90-94°C
^{1}H-NMR ($CDCl_3$) δ: 1.08 (3H, t, J = 8 Hz, CH_3), 1.30-1.80 (4H, m, CH_2CH_2), 1.80-2.40 (6H, m, $CH_2C{\equiv}C$), 3.37 (1H, brs, OH), 3.50-4.05 (2H, m, H-5'), 4.05-4.40 (2H, m, H-3', H-4'), 5.20 (1H, m, H-2'), 5.75 (2H, m, H-1', OH), 6.95-7.95 (3H, NH_2, OH), 7.72 (1H, s, H-8)

[0043]

Effect of the invention

The compounds of the present invention have high affinity for the A_2 receptor, but have low affinity for the A_1 receptor. Specifically, the compounds have high selectivity for the A_2 receptor. In addition, although the compounds exhibit dramatic

hypotensive function, they have low cardiac inhibition effects. Consequently, it is expected that these compounds will be used as drugs for circulatory diseases in order to treat or prevent hypertension, ischemic diseases (ischemic heart disease, ischemic brain disease) and other diseases.